AMENDMENT TO THE SPECIFICATION

Please replace the title on page 1 of the specification with the following title:
Methods for Treating Transplant Recipients with Humanized Immunoglobulins Reactive with B7 Molecules.

Please replace the paragraph on page 1, under the heading "Related Applications," with the following paragraph:

This application is a Continuation-In-Part of Application No. 09/339,596, filed June 24, 1999 (now U.S. Patent No. 6,913,747), which is a Continuation-In-Part of 09/249,011, filed February 12, 1999 (now U.S. Patent No. 6,972,125), the entire teachings of which are incorporated herein by reference.

Please replace the paragraphs beginning on page 8, line 14 through page 11, line 13, with the following paragraphs:

The invention relates to methods for treating an individual having a disease comprising administering an amount (e.g., therapeutically effective amount) of a humanized immunoglobulin specific to B7-1 and/or an amount (e.g., therapeutically effective amount) of a humanized immunoglobulin specific to B7-2. The diseases, as described herein, include, for example, autoimmune diseases, infectious diseases, asthma, inflammatory disorders, systemic lupus erythematosus, diabetes mellitus, insulitis, arthritis, inflammatory bowel disease, inflammatory dermatitis, and multiple sclerosis. This method also pertains to modulating the immune response of an individual having a transplanted organ, tissue, cell or the like comprising administering an effective amount of a humanized immunoglobulin that binds to B7-1 and/or a humanized immunoglobulin that binds to B7-2. This method further includes administering a drug that is used to modulate the immune response of an individual having a transplanted organ, tissue, cell or the like. The drug can be, for example, methotrexate, rapamycin, cyclosporin, steroids, anti-CD40 pathway inhibitors (e.g., anti-CD40 antibodies, anti-CD40 ligand antibodies and small molecule inhibitors of the CD40 pathway), transplant salvage pathway inhibitors (e.g., mycophenolate mofetil (MMF)), IL-2 receptor antagonists (e.g., ~~Zeonpax®~~ ZENAPAX® from Hoffmann-la Roche Inc., and ~~Simulet~~ SIMULECT® from Novartis, Inc.) and analogs thereof.

These drugs can be administered prior to, with or after administration of the humanized immunoglobulins.

The invention also pertains to methods for transplanting cells (e.g., bone marrow, blood cells, blood components and other cells) to an individual in need thereof comprising obtaining cells (e.g., bone marrow, or blood cells or components) from a donor, and contacting the cells with an immunoglobulin specific to B7-1 and/or an immunoglobulin specific to B7-2, and recipient cells, thereby obtaining a mixture. The immunoglobulins and the recipient cells are maintained for a period of time sufficient for tolerance induction. The mixture (referred to as a bone marrow composition or blood cell composition) is then introduced into the individual. The recipient cells can be lymphocytes (e.g. lymphocytes that express class 1 antigens (MHCI) or peripheral blood lymphocyte (PBL)). Instead of using recipient cells, the method also comprise utilizing tissue, organs or cells that express MHC Class I antigens, B7-1 and/or B7-molecules. The cells can be engineered to express recipient molecules. The cells from the donor can be bone marrow cells, or cells/components from blood (e.g., stem cells or immature cells). The B7 immunoglobulins are in contact with the donor bone marrow and the recipient cells for a period of time that is long enough to induce tolerance induction (e.g., about 1 to 96 hours, and, preferably about 36-48 hours). An individual in need of such a transplant is one who has a disease that is benefitted by or treatable with a bone marrow transplant. Such diseases, for example, are proliferative diseases (e.g. leukemia, lymphoma and cancer), anemia (e.g. sickle-cell anemia, thalassemia, and aplastic anemia), inborn errors of metabolism, congenital immunodeficiency diseases, and myeloid dysplasia syndrome (MDS). The method further includes administering to the individual a drug that is used to modulate the immune response (e.g., methotrexate; rapamycin; cyclosporin; steroids; anti-CD40 pathway inhibitors such as anti-CD40 antibodies, anti-CD40 ligand antibodies and small molecule inhibitors of the CD40 pathway; transplant salvage pathway inhibitors such as mycophenolate mofetil (MMF), IL-2 receptor antagonists such as ~~Zeonpax®~~ ZENAPAX® from Hoffmann-la Roche Inc., and ~~Simulet~~ SIMULECT® from Novartis, Inc.; or analogs thereof).

In particular, the invention includes methods for transplanting bone marrow to an individual having a disease (e.g., proliferative diseases such as leukemia, lymphoma, cancer; anemia such as sickle-cell anemia, thalassemia, and aplastic anemia; inborn errors of metabolism; congenital immunodeficiency diseases; and myeloid dysplasia syndrome) that is

treated with a bone marrow transplant comprising obtaining bone marrow from a donor, and contacting the bone marrow with immunoglobulins specific to B7-1 and/or an immunoglobulin specific to B7-2, and recipient cells (e.g., lymphocyte). The bone marrow, immunoglobulin(s) and recipient cells are in contact for a period of time sufficient for tolerance induction (e.g., about 1-96 hours, preferably about 36-48 hours). The method then comprises re-introducing the treated bone marrow to the individual. The method further includes administering to the individual a drug that is used to modulate the immune response (e.g., methotrexate; rapamycin; cyclosporin; steroids; anti-CD40 pathway inhibitors such as anti-CD40 antibodies, anti-CD40 ligand antibodies and small molecule inhibitors of the CD40 pathway; transplant salvage pathway inhibitors such as mycophenolate mofetil (MMF), IL-2 receptor antagonists such as ~~Zeonpax®~~ ZENAPAX® from Hoffmann-la Roche Inc., and ~~Simulet~~ SIMULECT® from Novartis, Inc.; or analogs thereof).

The invention also includes methods of treating a transplant recipient or preventing transplant rejection in a transplant recipient by administering to the recipient an effective amount of an immunoglobulin specific to B7-1 and/or an effective amount of an immunoglobulin specific to B7-2. The immunoglobulin specific to B7-1 is administered in an amount between about 1 mg/kg and 100 mg/kg, and the immunoglobulin specific to B7-2 is administered in an amount between about 1 mg/kg and about 100 mg/kg. The immunoglobulins specific to B7-1 and B7-2 can be administered on the day the recipient receives the transplantation (e.g., in an amount between about 1 mg/kg and about 25 mg/kg), and can also be administered periodically (e.g., daily, weekly or monthly) after the recipient receives the transplantation (e.g., in an amount between about 1 mg/kg and about 5 mg/kg). The method further includes administering a composition that is use in transplant rejection therapy, such as calcineurin inhibitors (e.g., cyclosporin A or FK506), steroids (e.g., methyl prednisone or prednisone), or immunosuppressive agents that arrest the growth of immune cells (e.g., rapamycin), anti-CD40 pathway inhibitors (e.g., anti-CD40 antibodies, anti-CD40 ligand antibodies and small molecule inhibitors of the CD40 pathway), transplant salvage pathway inhibitors (e.g., mycophenolate mofetil (MMF)), IL-2 receptor antagonists (e.g., ~~Zeonpax®~~ ZENAPAX® from Hoffmann-la Roche Inc., and ~~Simulet~~ SIMULECT® from Novartis, Inc.), or analogs thereof. Also, the present invention relates to a method of transplanting cells, tissue or organs to an individual in need thereof, by transplanting the cells, tissue or organs; and administering an effective amount of an

immunoglobulin specific to B7-1 and an effective amount of an immunoglobulin specific to B7-2 to the individual, as described above.

Please replace the paragraph beginning on page 47, lines 1-13, with the following paragraph:

The administration of the humanized B7-1 antibody, humanized B7-2 antibody and/or other drugs can occur simultaneously or sequentially in time. These compounds or compositions can be administered before, after or at the same time. Thus, the term "co-administration" is used herein to mean that the humanized B7-1 and/or B7-2 antibodies and/or other compositions are administered at times to treat the diseases described herein or induce tolerization (e.g., methotrexate; rapamycin; cyclosporin; steroids; anti-CD40 pathway inhibitors such as anti-CD40 antibodies, anti-CD40 ligand antibodies and small molecule inhibitors of the CD40 pathway; transplant salvage pathway inhibitors such as mycophenolate mofetil (MMF); IL-2 receptor antagonists such as ~~Zeonpax®~~ ZENAPAX® from Hoffmann-la Roche Inc. and ~~Simulet~~ SIMULECT® from Novartis, Inc. and analogs thereof). The methods of the present invention are not limited to the sequence in which the antibodies or compositions are administered, so long as they are administered close enough in time to produce the desired effect.

Please replace the paragraph beginning on page 60, line 26 through page 61, line 14, with the following paragraph:

The computer programs ABMOD and ~~ENCAD~~ ENCODE (Levitt *et al., J. Mol. Biol.* 168: 595 (1983)) were used to construct a molecular model of the 1F1 variable domain, which was used to locate the amino acids in the 1Fl framework that are close enough to the CDRs to potentially interact with them. To design the humanized 1F1 heavy and light chain variable regions, the CDRs from the mouse 1F1 heavy chain were grafted into the framework regions of the human III-2R heavy chain and the CDRs from the mouse 1Fl light chain were grafted into the framework regions of the human III-2R light chain. At framework positions where the computer model suggested significant contact with the CDRs, the amino acids from the mouse antibody were substituted for the original human framework amino acids. For humanized 1F1, this was done at residues 1, 24, 27, 28, 29, 30, 48, 67, and 68 of the heavy chain and at residues 47 and 72 of the light chain. Furthermore, framework residues that occurred only rarely at their

positions in the database of human antibodies were replaced by human consensus amino acids at those positions. For humanized 1F1 this was done at residues 16, 74, and 113 of the heavy chain and at residue 44 of the light chain. Overall, the humanized 1F1 heavy chain variable domain has 88 residues that are identical to the human III-2R heavy chain variable domain, and the humanized 1F1 light chain variable domain has 88 residues that are identical to the III-2R light chain variable domain.